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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,189	12/16/2005	Bjarne H. Dahl	2815-0335PUS1	3923

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EXAMINER	
CHUNG, SUSANNAH LEE	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
07/15/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/561,189	DAHL ET AL.	
	Examiner	Art Unit	
	SUSANNAH CHUNG	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/16/05, 9/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 9-12 are pending in the instant application. Claims 2-8 and 13 have been canceled by preliminary amendment.

Priority

This application is a 371 of PCT/EP04/51111, filed 06/15/2004.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by application no. PA 2003 00898 filed in the Denmark Patent Office on 06/17/2003, which papers have been placed of record in the file. The application names an inventor or inventors named in the prior application.

Information Disclosure Statement

The information disclosure statement(s) (IDS), filed on 12/16/05 and 9/29/06 have been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a

disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 11 and 12 of the present invention below:

(1) The Nature of the Invention

Claims 11 and 12 are directed to:

11. (previously presented) A method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to the blockade of chloride channels, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

12. (previously presented) The method according to claim 11, wherein the disease, disorder or condition responsive to the blockade of chloride channels is a bone metabolic disease, an osteoclast related bone disease, or a disease, disorder or condition that is responsive to inhibition of angiogenesis.

(2) The Breadth of the claims

Claims 11 and 12 will be given its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

In view of this rule, the claims will be interpreted (1) to be able to treat, prevent and alleviate, (2) all diseases or disorders of a living body, (3) wherein the disorder is responsive to the blockade of chloride channels. The breadth of dependent claim 12 is more narrow in that it specifies that the disease or disorder responsive to the blockage of chloride channels is a bone metabolic disease, an osteoclast related bone disease, or a disease that is responsive to inhibition of angiogenesis.

(3) The state of the prior art

Chloride channels serve a wide variety of specific cellular functions. They are found in every cell from bacteria to mammals. The pharmaceutical industry is investigating the potential use of chloride channel blockers for the treatment of various diseases.

There are many different types of compounds that can act as a chloride channel blocker. For example, Tamoxifen is a well known anti-cancer drug, but it is also being explored as a chloride channel blocker. Studies have shown that it reduces glutamate and

aspartate release from the ischemic cerebral cortex. This inhibition of the chloride channel could potential prevent cell swelling in the brain. (See Phillis et al., Brain Research, 780, 1998, 352-355, especially page 355.)

The state of the art at the time of this application was chloride channel blockers play a role in reducing cell swelling, but there is little data showing that a chloride channel blocker can alleviate a disorder, much less treat or prevent it.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether one of the compounds of the present invention could be reliably and predictably extrapolated to in vivo or in vitro activity in patients with any disorder related to inhibition of the chloride channel. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention states that the instantly claimed compounds could act as chloride channel blockers, but the specification does not provide any data to support this assertion. There is no biological data, such as in vitro or in vivo

data, population data, assays with inhibition data, or even any mention of a particular disorder that could be alleviated, treated or prevented.

(7) The presence or absence of working examples

In addition, the specification has no working examples of the role the instantly claimed compounds play as chloride channel blockers.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly claimed compounds as chloride channel blockers, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success.

In addition, the state of the art does not support the use of the instantly claimed tetrazole compounds for use as chloride channel blockers.

Obviousness Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 9, 10, 11 and 12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over

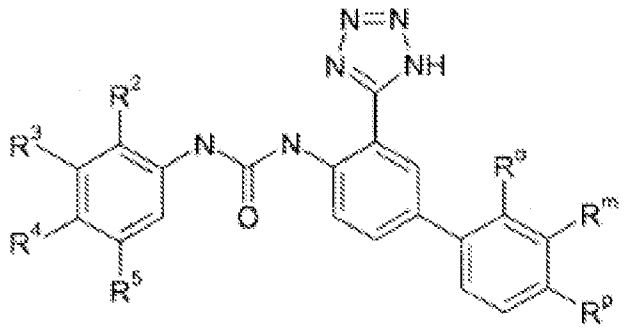
-Claims 1-15 of U.S. Patent Num. 6,297,261 B1 (`261 Patent);

-Claims 1-13 of U.S. Patent Num. 6,696,475 B2 (`475 Patent);

-Claims 12-20 of U.S. Patent App. Num. 2006/0058395 A1 (`395 App); and

-Claims 21-39 of U.S. Patent App. Num. 2006/0160856 A1 (`856 App).

Instant claims 1, 9 and 10 claim a compound and pharmaceutical composition of formula (I),



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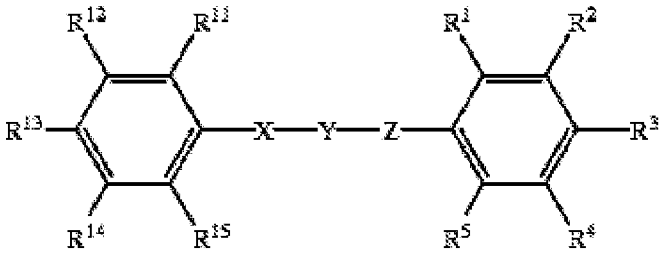
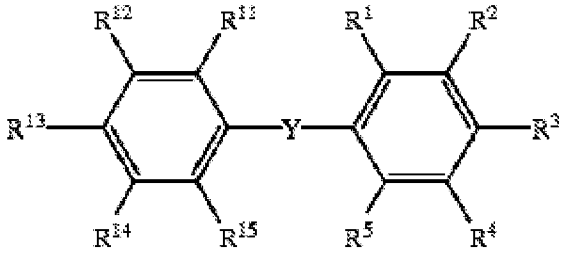
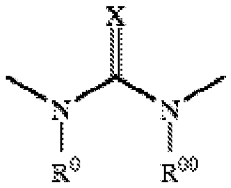
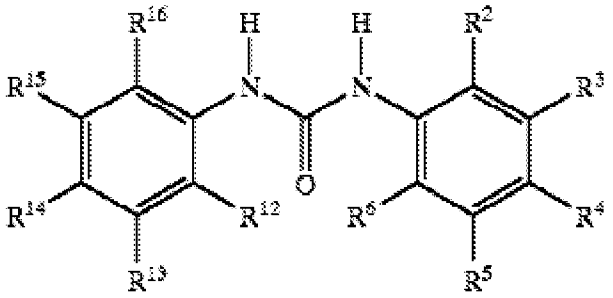
Instant claims 11 and 12 claim a method of treating, preventing and alleviating diseases or disorders, wherein the diseases or disorders are responsive to the blockade of chloride channels. The breadth of dependent claim 12 is more narrow in that it specifies

that the disease or disorder responsive to the blockage of chloride channels is a bone metabolic disease, an osteoclast related bone disease, or a disease that is responsive to inhibition of angiogenesis.

The `261 Patent claims a compound, composition and method of using a compound of formula  , wherein X and Z are NH; Y is CO; R1 is tetrazole; and R4 is phenyl, substituted with alkyl, hydroxyl, alkoxy, halogen, trifluoromethyl, or amino.

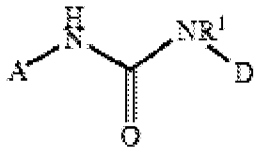
The `475 Patent claims a compound, composition and method of using a compound of formula,  , wherein Y is  , R1 is tetrazole, R12 and R14 are halo, trifluormethyl, trifluoromethoxy, alkyl, or alkoxy; and R4 is phenyl, substituted with halo, trifluormethyl, trifluoromethoxy, alkyl, amino, or alkoxy.

The `395 App. Claims methods of using a compound of formula

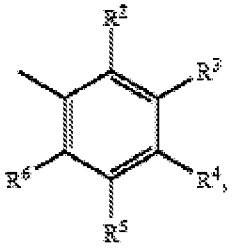


, wherein R2 is tetrazole, R4 is phenyl optionally substituted by halo, amino or trifluoromethyl; R13 and R16 are halo, trifluoromethyl, or alkyl.

The `856 App. Claims compounds, compositions and methods of using a compound of formula



, wherein A is phenyl, D is



, R2 is tetrazole, and R4 is phenyl substituted with amino.

The difference between `261 Patent, `475 Patent, `395 App, `856 App and the instantly claimed compounds is that prior patented or filed claims are broader than the instantly claimed compounds and in some cases the prior patented or filed claims have unsubstituted phenyl rings, while the instant application substituted with halogen or alkyl. Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that the prior patented and filed claims are the same compounds as the instantly claimed compounds. One of

ordinary skill in the art would be able to make and use the instantly claimed compounds from the disclosure of the prior patents and applications and vice versa. The slight variations in the substitution patterns, such as substituting methyl for hydrogen or fluorine for hydrogen is well known in the art. Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137. Fluorine and hydrogen are bioisosteres of one another. See Patani et al., Chem Rev., 1996, Vol. 96, No. 8, pages 3147-3176, especially page 3149. In addition, Patani teaches other bioisosteres, such as hydroxyl replacing amino (see page 3150). The motivation to optimize the methods of treating is that they will have similar pharmacological use.

Obviousness Double Patenting

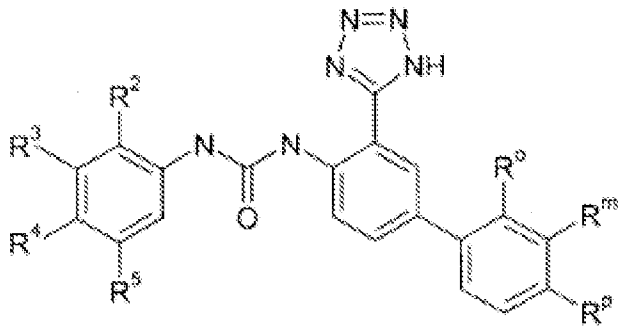
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

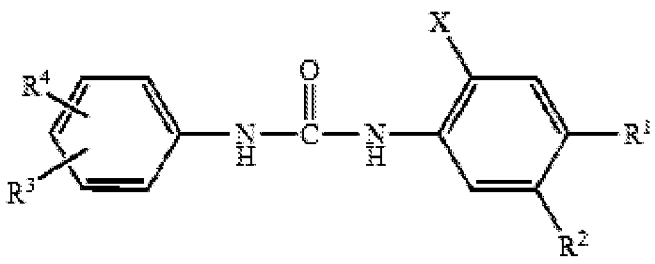
Claims 11 and 12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-41 of U.S. Patent App Num. 2007/0293553 A1 (`553 App).

Instant claims 11 and 12 claim a method of treating, preventing and alleviating diseases or disorders using a compound of formula



, wherein the diseases or disorders are responsive to the blockade of chloride channels. The breadth of dependent claim 12 is more narrow in that it specifies that the disease or disorder responsive to the blockage of chloride channels is a bone metabolic disease, an osteoclast related bone disease, or a disease that is responsive to inhibition of angiogenesis.

The `553 App. claims method of using a compound of formula



, wherein X is tetrazole, R2 is

halophenyl; haloalkyl-phenyl or haloalkoxy-phenyl; and R3 and R4 are alkyl, halo, haloalkyl, hydroxyl, alkoxy, or haloalkoxy.

The difference between the `553 App and the instantly claimed method is that the instantly claimed method is broader in scope than the `553 App.

Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that the `553 App methods and the instantly claimed methods are directed to the same therapeutic area. In addition, one of ordinary skill in the art would be able to make and use the instantly claimed compounds from the disclosure of the prior patents and applications and vice versa. The slight variations in the substitution patterns, such as substituting methyl for hydrogen or fluorine for hydrogen is well known in the art. Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137. Fluorine and hydrogen are bioisosteres of one another. See Patani et al., Chem Rev., 1996, Vol. 96, No. 8, pages 3147-3176, especially page 3149. In addition, Patani teaches other bioisosteres, such as hydroxyl replacing amino (see page 3150). The motivation to optimize the methods of treating is that they will have similar pharmacological use.

This is a provisional rejection. The instant application is senior and this rejection will be withdrawn should no other rejections remain.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1626

Susannah Chung, July 9, 2008